Search Strategy

```
     FILE 'USPATFULL' ENTERED AT 17:21:41 ON 26 JUN 2003

                  E SODROSKI JOSEPH G/IN
L1             13 S E3 OR E4
                  E WYATT RICHARD T/IN
                  E KWONG PETER D/IN
L2              1 S E3
                  E HENDRICKSON WAYNE A/IN
L3              5 S E2 OR E3

     FILE 'WPIDS' ENTERED AT 17:26:13 ON 26 JUN 2003

                  E SODROSKI J G/IN
L4             22 S E3

     FILE 'USPATFULL' ENTERED AT 17:28:52 ON 26 JUN 2003

                  E FARZAN M/IN
L5              1 S E4

     FILE 'MEDLINE' ENTERED AT 17:29:19 ON 26 JUN 2003

                  E SODROSKI J G/AU
L6            255 S E2-E5
L7            199 S L6 AND (LENTIVIR? OR HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L8            160 S L7 AND (ENV? OR GP160 OR GP120 OR GP41 OR SU OR TM)
                  E WYATT R T/AU
L9              3 S E3
                  E KWONG P D/AU
L10            21 S E3
L11            11 S L10 NOT L8
                  E HENDRICKSON W A/AU
L12           127 S E3
L13           120 S L12 NOT L8
L14             8 S L13 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                  E FARZAN M/AU
L15            32 S E3 OR E4
L16            14 S L15 NOT L8

     FILE 'USPATFULL' ENTERED AT 18:04:45 ON 26 JUN 2003

L17         25185 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L18         18150 S L17 AND (ENV? OR GP160 OR GP120 OR GP41 OR SU OR TM)
L19          1578 S L18 AND (ENV?/CLM OR GP160/CLM OR GP120/CLM OR GP41/CLM OR SU
L20           218 S L19 AND (DISULFIDE BOND?)
L21            31 S L20 AND (DISULFIDE/CLM OR CYSTEINE/CLM)
L22            29 S L21 NOT L1
L23           517 S L19 AND (HYDROPHOBIC)
L24           289 S L23 AND (MUTANT? OR MUTEIN?)
L25            23 S L24 AND HYDROPHOBIC/CLM
L26            23 S L25 NOT L1
L27           951 S L19 AND (PRO OR TURN)
L28             8 S L27 AND TURN/CLM
L29            56 S L27 AND PRO/CLM
```

```
L30          56 S L29 NOT L28
L31          83 S L19 AND (MUTANT?/CLM OR MUTEIN?/CLM)
L32           4 S L19 AND (CD4BS OR CD4I)

     FILE 'MEDLINE' ENTERED AT 18:19:14 ON 26 JUN 2003

L33      131923 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L34       28895 S L33 AND (ENV? OR GP160 OR GP120 OR GP41 OR SU OR TM)
L35          77 S L34 AND (DISULFIDE BOND?)
L36          73 S L35 NOT L8
L37         105 S L34 AND CAVIT?
L38         105 S L37 NOT L36
L39         287 S L34 AND TURN?
L40          21 S L39 AND (PRO OR PROLINE)
L41          22 S L34 AND (CD4BS OR CD4I)
L42           8 S L41 AND CD4I
L43        1192 S L34 AND (MUTANT? OR MUTEIN? OR MODIFICATION? OR MUTAGENESIS)
L44          35 S L43 AND (AMINO ACID CHANGES OR CHANGES IN AMINO ACIDS OR STRU
```

L1 ANSWER 1 OF 13 USPATFULL
2003:126732 Stabilization of envelope glycoprotein trimers by disulfide bonds introduced into a gp41 glycoprotein ectodomain.
Sodroski, Joseph G., Medford, MA, UNITED STATES
Farzan, Michael, Brookline, MA, UNITED STATES
US 2003086943 A1 20030508
APPLICATION: US 2002-179152 A1 20020625 (10)
PRIORITY: US 1997-60808P 19971003 (60)
US 1997-60813P 19971001 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present application is directed to stabilized envelope glycoprotein trimers. The trimers are stabilized by introducing disulfide bonds at certain sites in the gp41 ectodomain. DNA molecules encoding such trimers can be used to generate an immunogenic reaction.

CLM What is claimed is:
1. An isolated molecule containing a nucleotide sequence encoding an HIV-1 or HIV-2 envelope glycoprotein containing at least the coiled coil portion of the gp41 transmembrane envelope glycoprotein, wherein cysteine residues are introduced at residues adjacent to a d and e position of the coiled coil helix, and a gp120 glycoprotein or gp120 derivative, wherein the gp120 derivative contains multiple gp120 constant regions connected by variable regions and/or linker residues that permit potential turns in the polypeptide structure so the derivative maintains a conformation approximating that of wild type gp120, wherein at least a portion of one variable region has been deleted.

2. The isolated molecule of claim 1 wherein the gp120 glycoprotein or derivative is the gp120 derivative.

3. The isolated molecule of claim 2, wherein the gp120 derivative lacks portions of at least the V1, V2, C1 and/or C5 regions.

4. The isolated molecule of claim 3, wherein the gp120 derivative is a HIV-1 gp120 derivative.

5. The isolated molecule of claim 1, wherein the nucleotide sequence is a DNA sequence.

6. An isolated and purified protein encoded by the nucleotide sequence of claim 1.

7. The protein of claim 6, wherein the d and e position, d/e, correspond to sites numbered 555/556, 562/563, 569/570, 576/577 or 583/584 in the HxBc2 HIV-1 strain.

8. The protein of claim 6, wherein a gly is substituted for ala at position f.

9. The protein of claim 8, wherein the f position corresponds to sites numbered 557, 564, 571, 578 and 584 of the HxBc2 HIV-1 strain, respectively.

10. The protein of claim 8, wherein the sites are the d, e and f positions correspond to sites 576, 577 and 578, respectively, of the HxBc2 HIV-1 strain.

11. A vector containing the nucleotide sequence of claim 1 operably linked to a promoter.

12. The vector of claim 11, wherein the vector is a viral vector.

13. A pharmaceutical composition containing (a) the purified protein of claim 6 or a nucleotide molecule encoding said purified protein, and (b) a pharmaceutically acceptable carrier or diluent.

14. A method of generating an immune reaction comprising administering an immunogen-stimulating amount of the protein of claim 6 and an adjuvant to an animal.

15. A method of generating an immune reaction comprising administering an immunogen-stimulating amount of the DNA sequence of claim 1.

L3 ANSWER 2 OF 5 USPATFULL
2002:308321 Compounds which bind to the central cavity between HIV-1 gp120 and CD4 and uses thereof.
Kwong, Peter, New York, NY, UNITED STATES
Hendrickson, Wayne, New York, NY, UNITED STATES
Wyatt, Richard, Andover, MA, UNITED STATES
Sodroski, Joseph, Medford, MA, UNITED STATES
US 2002173446 A1 20021121
APPLICATION: US 2001-12507 A1 20011207 (10)
PRIORITY: US 2000-254046P 20001207 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a method for identifying a compound which inhibits HIV-1 entry into a cell. This invention also provides a compound which inhibits the cavity binding interaction between HIV-1 gp120 and CD4. This invention further provides a method of inhibiting HIV-1 infection of a cell, a method of preventing HIV-1 infection in a subject and a method of treating HIV-1 infection in a subject comprising contacting the cell or administering to the subject an amount of the compound which inhibits the cavity binding interaction between HIV-1 gp120 and CD4 effective to inhibit HIV-1 infection, thereby inhibiting HIV-1 infection of the cell, preventing HIV-1 infection in the subject and treating HIV-1 infection in the subject.

CLM What is claimed is:
1. A method for identifying a compound which inhibits HIV-1 entry into a cell: (a) determining the conformation of a crystal of the central cavity of HIV-1 gp120 in the presence of a ligand; (b) contacting the crystal of HIV-1 gp120 with the compound; (c) determining the conformation of the crystalized HIV-1 gp120 central cavity in the presence of the compound; and (d) comparing the conformation of the crystalized HIV-1 gp120 central cavity determined in step (c) with the conformation of the crystalized HIV-1 gp120 in step (a) so as to identify a compound which inhibits HIV-1 entry into the cell.

2. The method of claim 1, wherein the ligand in step (a) is soluble CD4 or a soluble CD4 mimetic.

3. A compound identified by the method of claim 1.

4. A composition which comprises the compound of claim 3 and a carrier.

5. The composition of claim 4, wherein the carrier is a diluent, an aerosol, a topical carrier, an aqueous solution, a nonaqueous or a solid

carrier.

6. A compound which inhibits the cavity binding interaction between HIV-1 gp120 and CD4.

7. A method of inhibiting HIV-1 infection of a cell comprising contacting the cell with an amount of the compound of claim 3 effective to inhibit HIV-1 infection, thereby inhibiting HIV-1 infection of the cell.

8. A method of preventing HIV-1 infection in a subject comprising administering to the subject an amount of the compound of claim 3 effective to inhibit HIV-1 infection, thereby preventing HIV-1 infection in the subject.

9. A method of treating HIV-1 infection in a subject comprising administering to the subject an amount of the compound of claim 3 effective to inhibit HIV-1 infection, thereby treating HIV-1 infection in the subject.

10. A method of inhibiting HIV-1 infection of a cell comprising contacting the cell with an amount of the compound of claim 6 effective to inhibit HIV-1 infection, thereby inhibiting HIV-1 infection of the cell.

11. A method of preventing HIV-1 infection in a subject comprising administering to the subject an amount of the compound of claim 6 effective to inhibit HIV-1 infection, thereby preventing HIV-1 infection in the subject.

12. A method of treating HIV-1 infection in a subject comprising administering to the subject an amount of the compound of claim 6 effective to inhibit HIV-1 infection, thereby treating HIV-1 infection in the subject.

L30 ANSWER 34 OF 56 USPATFULL
1999:166839 Retroviral envelopes having modified hypervariable polyproline regions.
Anderson, W. French, San Marino, CA, United States
Wu, Bonnie Weimin, Pasadena, CA, United States
University of Southern California, Los Angeles, CA, United States (U.S. corporation)
US 6004798 19991221
APPLICATION: US 1997-856074 19970514 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A retroviral vector particle having a modified retroviral envelope polypeptide. The retroviral envelope polypeptide includes the hypervariable polyproline region, or hinge region, and the hypervariable polyproline region, or hinge region is modified to include a targeting polypeptide including a binding region which binds to a ligand. Such a retroviral vector may be "targeted" to various cells for delivery of genetic material to such cells.

CLM What is claimed is:
1. A retroviral vector particle having a modified retroviral envelope polypeptide, said retroviral envelope polypeptide including the hypervariable polyproline region, wherein said hypervariable polyproline region is modified to include a targeting polypeptide including a binding region which binds to a ligand, and said

retroviral vector particle including at least one polynucleotide encoding a therapeutic agent.

2. The retroviral vector particle of claim 1 wherein prior to modification the hypervariable polyproline region of said envelope has the sequence (SEQ ID NO:1), and in the modified polypeptide, amino acid residues 34 through 49 of (SEQ ID NO:1) are removed and replaced with the targeting polypeptide.

3. The retroviral vector particle of claim 1 wherein prior to modification the hypervariable polyproline region of said envelope has the sequence (SEQ ID NO:1), and in the modified polypeptide, amino acid residue 35 is changed from asparagine to glutamine, amino acid residue 48 is changed from threonine to glycine, and amino acid residue 49 is changed from serine to leucine, and the targeting polypeptide is inserted between amino acid residues 35 and 36 of (SEQ ID NO:1).

4. The retroviral vector particle of claim 1 wherein said ligand is an extracellular matrix component.

5. The retroviral vector particle of claim 4 wherein said extracellular matrix component is collagen.

6. The retroviral vector particle of claim 5 wherein said binding region which binds to collagen has the following structure: Trp-Arg-Glu-Pro-Ser-Phe-Met-Ala-Leu-Ser.

7. A modified polynucleotide encoding a modified retroviral envelope polypeptide, said retroviral envelope polypeptide including the hypervariable polyproline region, wherein, prior to modification, the polynucleotide encoding the hypervariable polyproline region encodes a hypervariable polyproline region having the sequence (SEQ ID NO:1), and in the modified polynucleotide, the codons encoding amino acid residues 34 through 49 of (SEQ ID NO:1) are removed and replaced with the polynucleotide encoding said targeting polypeptide.

8. A retroviral plasmid vector including the modified polynucleotide of claim 7.

9. A producer cell for producing a retroviral vector particle having a modified envelope polypeptide, said producer cell including the modified polynucleotide of claim 7.

10. A method of generating retroviral vector particles, comprising: (a) transfecting a cell line selected from the group consisting of (i) a pre-packaging cell line including polynucleotides encoding the gag and pol retroviral proteins; and (ii) a packaging cell line including polynucleotides encoding the gag, pol, and env retroviral proteins with the retroviral plasmid vector of claim 8 to form a producer cell line; (b) culturing said producer cell line to generate retroviral vector particles; and (c) recovering said retroviral vector particles generated from said producer cell line.

11. A modified polynucleotide encoding a modified retroviral envelope polypeptide, said retroviral envelope polypeptide including the hypervariable polyproline region, wherein, prior to modification, the polynucleotide encoding the hypervariable polyproline region encodes a hypervariable polyproline region having the sequence (SEQ ID NO:1), and in the modified polynucleotide, the codon

encoding amino acid residue 35 is changed such that the codon encoding amino acid residue 35 encodes glutamate, the codon encoding amino acid residue 48 is changed such that the codon encoding amino acid residue 48 encodes glycine, and the codon encoding amino acid residue 49 is changed such that the codon encoding amino acid residue 49 encodes leucine, and the polynucleotide encoding the targeting polypeptide is inserted between the codon encoding amino acid residue 35 and the codon encoding amino acid residue 36 of (SEQ ID NO: 1).

12. A retroviral plasmid vector including the modified polynucleotide of claim 11.

13. A producer cell for producing a retroviral vector particle having a modified envelope polypeptide, said producer cell including the modified polynucleotide of claim 11.

14. A method of generating retroviral vector particles, comprising: (a) transfecting a cell line selected from the group consisting of (i) a pre-packaging cell line including polynucleotides encoding the gag and pol retroviral proteins; and (ii) a packaging cell line including polynucleotides encoding the gag, pol, and env retroviral proteins with the retroviral plasmid vector of claim 12 to form a producer cell line; (b) culturing said producer cell line to generate retroviral vector particles; and (c) recovering said retroviral vector particles generated from said producer cell line.

L4 ANSWER 1 OF 22 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-583669 [62] WPIDS
DNC C2002-165081
TI New stable immunogenic proteoliposome containing a transmembrane protein, useful as an immunogen for eliciting immune reaction (e.g. against an HIV infection), in drug screening assays or for identifying ligands.
DC B04 D16
IN GRUNDER, C; MIRZABEKOV, T; SODROSKI, J G; WYATT, R T
PA (DAND) DANA FARBER CANCER INST INC
CYC 100
PI WO 2002056831 A2 20020725 (200262)* EN 92p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
ADT WO 2002056831 A2 WO 2001-US50820 20011227
PRAI US 2000-258438P 20001227

AB WO 200256831 A UPAB: 20020926
NOVELTY - A stable immunogenic proteoliposome, which comprises a spherical or elliptoid shape having a ligand to an immunogenic transmembrane protein anchored to the shape, and an isolated integral membrane protein bound to the ligand, is new.

DETAILED DESCRIPTION - A stable immunogenic proteoliposome, which comprises a spherical or elliptoid shape having a ligand to an immunogenic transmembrane protein anchored to the shape, and an isolated integral membrane protein bound to the ligand, is new. The shape's surface is surrounded by a lipid membrane. The integral membrane protein's transmembrane domains are in the lipid membrane. The immunogenic transmembrane protein is a multimer and has a wild type conformation.

INDEPENDENT CLAIMS are also included for the following:

(1) a method of obtaining an antibody to an envelope glycoprotein by screening a library of antibodies with the immunogenic proteoliposome; and selecting antibodies that bind to the proteoliposome; and

(2) methods of inducing an immunogenic response to an HIV-1 virion comprising:

(a) administering the immunogenic proteoliposome to a human, and subsequent boosting amounts of the immunogenic proteoliposome or envelope afterwards at periodic times; or

(b) administering to a human the antibody obtained in the method above.

ACTIVITY - Immunostimulant; Virucide.

MECHANISM OF ACTION - None given. No biodata is provided in the source material.

USE - The proteoliposome is useful as an immunogen for eliciting immune reaction, e.g. against an HIV infection. It is also useful in screening assays (e.g. as antigens for screening antibody libraries), drug screening or for identifying ligands.

Dwg.0/18

L8 ANSWER 10 OF 160 MEDLINE
2002465868 Document Number: 22199155. PubMed ID: 12208966. Mutagenic stabilization and/or disruption of a CD4-bound state reveals distinct conformations of the human immunodeficiency virus type 1 gp120 envelope glycoprotein.
Xiang Shi-Hua; Kwong Peter D; Gupta Rishi; Rizzuto Carlo D; Casper David J; Wyatt Richard; Wang Liping; Hendrickson Wayne A; Doyle Michael L; Sodroski Joseph. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute and Harvard Medical School. Boston, Massachusetts 02115, USA.) JOURNAL OF VIROLOGY, (2002 Oct) 76 (19) 9888-99. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The human immunodeficiency virus type 1 (HIV-1) gp120 exterior envelope glycoprotein is conformationally flexible. Upon binding to the host cell receptor CD4, gp120 assumes a conformation that is recognized by the second receptor, CCR5 and/or CXCR4, and by the CD4-induced (CD4i) antibodies. Guided by the X-ray crystal structure of a gp120-CD4-CD4i antibody complex, we introduced changes into gp120 that were designed to stabilize or disrupt this conformation. One mutant, 375 S/W, in which the tryptophan indole group is predicted to occupy the Phe 43 cavity in the gp120 interior, apparently favors a gp120 conformation closer to that of the CD4-bound state. The 375 S/W mutant was recognized as well as or better than wild-type gp120 by CD4 and CD4i antibodies, and the large decrease in entropy observed when wild-type gp120 bound CD4 was reduced for the 375 S/W mutant. The recognition of the 375 S/W mutant by CD4BS antibodies, which are directed against the CD4-binding region of gp120, was markedly reduced compared with that of the wild-type gp120. Compared with the wild-type virus, viruses with the 375 S/W envelope glycoproteins were resistant to neutralization by IgG1b12, a CD4BS antibody, were slightly more sensitive to soluble CD4 neutralization and were neutralized more efficiently by the 2G12 antibody. Another mutant, 423 I/P, in which the gp120 bridging sheet was disrupted, did not bind CD4, CCR5, or CD4i antibodies, even though recognition by CD4BS antibodies was efficient. These results indicate that CD4BS antibodies recognize conformations of gp120 different from that recognized by CD4 and CD4i antibodies.

L8 ANSWER 33 OF 160 MEDLINE
2000240060 Document Number: 20240060. PubMed ID: 10775613. Modifications that stabilize human immunodeficiency virus envelope glycoprotein trimers in solution. Yang X; Florin L; Farzan M; Kolchinsky P; Kwong P D; Sodroski J; Wyatt R. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Harvard Medical School, Harvard School of Public Health, Boston, Massachusetts 02115, USA.) JOURNAL OF VIROLOGY, (2000 May) 74 (10) 4746-54. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The functional unit of the human immunodeficiency virus type 1 (HIV-1) envelope glycoproteins is a trimer composed of three gp120 exterior glycoproteins and three gp41 transmembrane glycoproteins. The lability of intersubunit interactions has hindered the production and characterization of soluble, homogeneous envelope glycoprotein trimers. Here we report three modifications that stabilize soluble forms of HIV-1 envelope glycoprotein trimers: disruption of the proteolytic cleavage site between gp120 and gp41, introduction of

cysteines that form intersubunit disulfide bonds, and addition of GCN4 trimeric helices. Characterization of these secreted glycoproteins by immunologic and biophysical methods indicates that these stable trimers retain structural integrity. The efficacy of the GCN4 sequences in stabilizing the trimers, the formation of intersubunit disulfide bonds between appropriately placed cysteines, and the ability of the trimers to interact with a helical, C-terminal gp41 peptide (DP178) support a model in which the N-terminal gp41 coiled coil exists in the envelope glycoprotein precursor and contributes to intersubunit interactions within the trimer. The availability of stable, soluble HIV-1 envelope glycoprotein trimers should expedite progress in understanding the structure and function of the virion envelope glycoprotein spikes.

L8 ANSWER 55 OF 160 MEDLINE
1998362173 Document Number: 98362173. PubMed ID: 9696864. Stabilization of human immunodeficiency virus type 1 envelope glycoprotein trimers by disulfide bonds introduced into the gp41 glycoprotein ectodomain. Farzan M; Choe H; Desjardins E; Sun Y; Kuhn J; Cao J; Archambault D; Kolchinsky P; Koch M; Wyatt R; Sodroski J. (Division of Human Retrovirology, Dana-Farber Cancer Institute, and Department of Pathology, Harvard Medical School, Boston, Massachusetts 02115, USA.. farzan@mbcrr.harvard.edu) . JOURNAL OF VIROLOGY, (1998 Sep) 72 (9) 7620-5. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Biochemical and structural studies of fragments of the ectodomain of the human immunodeficiency virus type 1 (HIV-1) gp41 transmembrane envelope glycoprotein have demonstrated that the molecular contacts between alpha helices allow the formation of a trimeric coiled coil. By introducing cysteine residues into specific locations along these alpha helices, the normally labile HIV-1 gp160 envelope glycoprotein was converted into a stable disulfide-linked oligomer. Although proteolytic cleavage into gp120 and gp41 glycoproteins was largely blocked, the disulfide-linked oligomer was efficiently transported to the cell surface and was recognized by a series of conformationally dependent antibodies. The pattern of hetero-oligomer formation between this construct and an analogous construct lacking portions of the gp120 variable loops and of the gp41 cytoplasmic tail demonstrates that these oligomers are trimers. These results support the relevance of the proposed gp41 structure and intersubunit contacts to the native, complete HIV-1 envelope glycoprotein. Disulfide-mediated stabilization of the labile HIV-1 envelope glycoprotein oligomer, which has been suggested to possess advantages as an immunogen, may assist attempts to develop vaccines.

L8 ANSWER 58 OF 160 MEDLINE
1998303386 Document Number: 98303386. PubMed ID: 9641684. The antigenic structure of the HIV gp120 envelope glycoprotein. Wyatt R; Kwong P D; Desjardins E; Sweet R W; Robinson J; Hendrickson W A; Sodroski J G. (Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.) NATURE, (1998 Jun 18) 393 (6686) 705-11. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The human immunodeficiency virus HIV -1 establishes persistent infections in humans which lead to acquired immunodeficiency syndrome (AIDS). The HIV-1 envelope

glycoproteins, gp120 and gp41, are assembled into a trimeric complex that mediates virus entry into target cells. HIV -1 entry depends on the sequential interaction of the gp120 exterior envelope glycoprotein with the receptors on the cell, CD4 and members of the chemokine receptor family. The gp120 glycoprotein, which can be shed from the envelope complex, elicits both virus-neutralizing and non-neutralizing antibodies during natural infection. Antibodies that lack neutralizing activity are often directed against the gp120 regions that are occluded on the assembled trimer and which are exposed only upon shedding. Neutralizing antibodies, by contrast, must access the functional envelope glycoprotein complex and typically recognize conserved or variable epitopes near the receptor-binding regions. Here we describe the spatial organization of conserved neutralization epitopes on gp120, using epitope maps in conjunction with the X-ray crystal structure of a ternary complex that includes a gp120 core, CD4 and a neutralizing antibody. A large fraction of the predicted accessible surface of gp120 in the trimer is composed of variable, heavily glycosylated core and loop structures that surround the receptor-binding regions. Understanding the structural basis for the ability of HIV-1 to evade the humoral immune response should assist in the design of a vaccine.

L8 ANSWER 85 OF 160 MEDLINE
96344034 Document Number: 96344034. PubMed ID: 8726523. Conformation of the HIV-1 gp 120 envelope glycoprotein. Sodroski J; Wyatt R; Olshevsky U; Olshevsky V; Moore J. (Dana-Farber Cancer Institute, Department of Pathology, Harvard Medical School, Boston, Mass., USA.) ANTIBIOTICS AND CHEMOTHERAPY, (1996) 48 184-7. Ref: 7. Journal code: 1305576. ISSN: 0066-4758. Pub. country: Switzerland. Language: English.

L8 ANSWER 116 OF 160 MEDLINE
94112125 Document Number: 94112125. PubMed ID: 7904352. Towards a structure of the HIV-1 envelope glycoprotein gp120: an immunochemical approach. Moore J P; Jameson B A; Sattentau Q J; Willey R; Sodroski J. (Aaron Diamond AIDS Research Center, New York University School of Medicine, New York 10016.) PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY OF LONDON. SERIES B: BIOLOGICAL SCIENCES, (1993 Oct 29) 342 (1299) 83-8. Journal code: 7503623. ISSN: 0962-8436. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The HIV-1 surface glycoprotein gp120 binds CD4 in the initial state of virus-cell fusion. The extensive glycosylation of gp120 has thus far precluded definition of its structure by crystallographic methods. As an initial approach to a gp120 structure, the surface topology was mapped using antibodies. First, the regions of gp120 that are accessible on the surface of the native molecule, and those that are internal but exposed after denaturation, are identified. Second, epitopes for antibodies that recognize complex surface structures comprising segments of different domains are identified. Third, we define how mutations in one domain of gp120 influence the binding of antibodies to defined epitopes on other domains. These latter approaches enable us to start to understand the inter-domain interactions that contribute to the overall structure of the gp120 molecule. Information from these studies is being used to model the structures of individual gp120 domains, and the way in which these interact in the folded protein.

L8 ANSWER 122 OF 160 MEDLINE

93267832 Document Number: 93267832. PubMed ID: 8497077. Effect of amino acid changes in the V1/V2 region of the human immunodeficiency virus type 1 gp120 glycoprotein on subunit association, syncytium formation, and recognition by a neutralizing antibody. Sullivan N; Thali M; Furman C; Ho D D; Sodroski J. (Division of Human Retrovirology, Dana-Farber Cancer Institute, New York, New York.) JOURNAL OF VIROLOGY, (1993 Jun) 67 (6) 3674-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The contributions of the first and second variable regions of the human immunodeficiency virus type 1 gp120 glycoprotein to envelope glycoprotein structure, function, and recognition by a neutralizing antibody were studied. **Several mutants with substitutions in the V2 loop demonstrated complete dissociation of the gp120 and gp41 glycoproteins, suggesting that inappropriate changes in V2 conformation can affect subunit assembly.** Some glycoproteins with changes in V1 or V2 were efficiently expressed on the cell surface and were able to bind CD4 but were **deficient in syncytium formation and/or virus entry.** Recognition of gp120 by the neutralizing monoclonal antibody G3-4 was affected by particular substitutions affecting residues 176 to 184 in the V2 loop. These results suggest that the V1/V2 variable regions of the human immunodeficiency virus type 1 gp120 glycoprotein play a role in postreceptor binding events in the membrane fusion process and can act as a target for neutralizing antibodies.

L8 ANSWER 123 OF 160 MEDLINE

93233242 Document Number: 93233242. PubMed ID: 8474172. Effects of amino acid changes in the extracellular domain of the human immunodeficiency virus type 1 gp41 envelope glycoprotein. Cao J; Bergeron L; Helseth E; Thali M; Repke H; Sodroski J. (Division of Human Retrovirology, Dana-Farber Cancer Institute, Boston, Massachusetts.) JOURNAL OF VIROLOGY, (1993 May) 67 (5) 2747-55. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Changes were introduced into conserved amino acids within the ectodomain of the human immunodeficiency virus type 1 (HIV-1) gp41 transmembrane envelope glycoprotein. The effect of these changes on the structure and function of the HIV-1 envelope glycoproteins was examined. The gp41 glycoprotein contains an amino-terminal fusion peptide (residues 512 to 527) and a disulfide loop near the middle of the extracellular domain (residues 598 to 604). Mutations affecting the hydrophobic sequences between these two regions resulted in two phenotypes. Some **changes in amino acids 528 to 562 resulted in a loss of the noncovalent association between gp41 and the gp120 exterior glycoprotein. Amino acid changes in other parts of the gp41 glycoprotein (residues 608 and 628) also resulted in subunit dissociation. Some changes affecting amino acids 568 to 596 resulted in envelope glycoproteins partially or completely defective in mediating membrane fusion.** Syncytium formation was more sensitive than virus entry to these changes. Changes in several amino acids from 647 to 675 resulted in higher-than-wild-type syncytium-forming ability. One of these amino acid changes affecting tryptophan 666 resulted in escape from neutralization by an anti-gp41 human monoclonal antibody, 2F5. These results contribute to an understanding of the functional regions of the HIV-1 gp41 ectodomain.

L8 ANSWER 136 OF 160 MEDLINE
92148651 Document Number: 92148651. PubMed ID: 1738091. Contribution of disulfide bonds in the carboxyl terminus of the human immunodeficiency virus type I gp120 glycoprotein to CD4 binding. Lekutis C; Olshevsky U; Furman C; Thali M; Sodroski J. (Dana-Farber Cancer Institute, Department of Pathology, Harvard Medical School, Boston, Massachusetts 02115.) JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES, (1992) 5 (1) 78-81. Journal code: 8812597. ISSN: 0894-9255. Pub. country: United States. Language: English.

AB The carboxyl half of the HIV-1 gp120 glycoprotein, which has been implicated in binding to the CD4 receptor, contains two disulfide bonds linking cysteine residues 378-445 and 385-418. To examine the necessity of these disulfide bonds for the formation and/or maintenance of a gp120 glycoprotein competent for CD4 binding, we created mutants of a soluble form of gp120 in which combinations of these cysteine residues were altered. The mutant glycoproteins were examined for export from the expressing cell and for CD4 binding ability. Mutant gp120 molecules lacking both disulfide bonds were not stably expressed or exported. However, mutants for which either disulfide bond could form were exported and were fully competent for CD4 binding. In some cases, the presence of one of the pair of linked cysteines exerted more detrimental effects on export or CD4 binding than did alteration of both cysteines. Thus, the evaluation or the contribution of a particular disulfide bond to a phenotype should include studies in which both cysteines involved in the bond are simultaneously altered.

L8 ANSWER 144 OF 160 MEDLINE
91056608 Document Number: 91056608. PubMed ID: 2243396. Changes in the transmembrane region of the human immunodeficiency virus type 1 gp41 envelope glycoprotein affect membrane fusion. Helseth E; Olshevsky U; Gabuzda D; Ardman B; Haseltine W; Sodroski J. (Dana-Farber Cancer Institute, Department of Pathology, Harvard Medical School, Boston, Massachusetts.) JOURNAL OF VIROLOGY, (1990 Dec) 64 (12) 6314-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The charged amino acids near or within the membrane-spanning region of the human immunodeficiency virus type 1 gp41 envelope glycoprotein were altered. **Two mutants were defective for syncytium formation and virus replication** even though levels of envelope glycoproteins on the cell or virion surface and CD4 binding were comparable to those of the wild-type proteins. Thus, in addition to anchoring the envelope glycoproteins, sequences proximal to the membrane-spanning gp41 region are important for the membrane fusion process.

L36 ANSWER 2 OF 73 MEDLINE
2003199891 Document Number: 22605469. PubMed ID: 12719576. Human immunodeficiency virus type 1 Env with an intersubunit disulfide bond engages coreceptors but requires bond reduction after engagement to induce fusion. Abrahamyan L G; Markosyan R M; Moore J P; Cohen F S; Melikyan G B. (Department of Molecular Biophysics and Physiology, Rush Medical College, Chicago, Illinois 60612, USA.) JOURNAL OF VIROLOGY, (2003 May) 77 (10) 5829-36. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB A mutant human immunodeficiency virus (

HIV) envelope protein (Env) with **an engineered disulfide bond** between the gp120 and gp41 subunits (SOS-Env) was expressed on cell surfaces. With the disulfide bond intact, **these cells did not fuse to target cells expressing CD4 and CCR5**, but the fusion process did advance to an intermediate state: cleaving the disulfide bond with a reducing agent after but not before binding to target cells allowed fusion to occur. Through the use of an antibody directed against CCR5, it was found that at the intermediate stage, SOS-Env had associated with coreceptors. Reducing the disulfide bond after this intermediate had been reached resulted in hemifusion at low temperature and fusion at physiological temperature. The addition of C34 or N36, peptides that prevent six-helix bundle formation, at the hemifused state blocked the fusion that would have resulted after raising the temperature. Thus, Env has not yet folded into six-helix bundles after hemifusion has been achieved. Because SOS-Env binds CCR5, it is suggested that the conformational changes in wild-type Env that result from this binding cause disengagement of gp120 from gp41 in the region of the engineered bond. It is proposed that this disengagement is the event that directly frees gp41 to undergo the conformational changes that lead to fusion. The intermediate state achieved prior to reduction of the disulfide bond was stable. The capture of this configuration of Env could yield a suitable antigen for vaccine development, and it may also be a target for pharmacological intervention against HIV-1 entry.

L36 ANSWER 15 OF 73 MEDLINE
2001349990 Document Number: 21306366. PubMed ID: 11413331. Functional analysis of the disulfide-bonded loop/chain reversal region of human immunodeficiency virus type 1 gp41 reveals a critical role in gp120-gp41 association. Maerz A L; Drummer H E; Wilson K A; Poumbourios P. (St. Vincent's Institute of Medical Research, Fitzroy, Victoria 3065, Australia.) JOURNAL OF VIROLOGY, (2001 Jul) 75 (14) 6635-44. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Human immunodeficiency virus type 1 (HIV-1) entry into cells is mediated by the surface-exposed envelope protein (SU) gp120, which binds to cellular CD4 and chemokine receptors, triggering the membrane fusion activity of the transmembrane (TM) protein gp41. The core of gp41 comprises an N-terminal triple-stranded coiled coil and an antiparallel C-terminal helical segment which is packed against the exterior of the coiled coil and is thought to correspond to a fusion-activated conformation. The available gp41 crystal structures lack the conserved disulfide-bonded loop region which, in human T-lymphotropic virus type 1 (HTLV-1) and murine leukemia virus TM proteins, mediates a chain reversal, connecting the antiparallel N- and C-terminal regions. Mutations in the HTLV-1 TM protein gp21 disulfide-bonded loop/chain reversal region adversely affected fusion activity without abolishing SU-TM association (A. L. Maerz, R. J. Center, B. E. Kemp, B. Kobe, and P. Poumbourios, J. Virol. 74:6614-6621, 2000). We now report that in contrast to our findings with HTLV-1, conservative substitutions in the HIV-1 gp41 disulfide-bonded loop/chain reversal region abolished association with gp120. While the mutations affecting gp120-gp41 association also affected cell-cell fusion

activity, HIV-1 glycoprotein maturation appeared normal. The mutant glycoproteins were processed, expressed at the cell surface, and efficiently immunoprecipitated by conformation-dependent monoclonal antibodies. The gp120 association site includes aromatic and hydrophobic residues on either side of the gp41 disulfide-bonded loop and a basic residue within the loop. The HIV-1 gp41 disulfide-bonded loop/chain reversal region is a critical gp120 contact site; therefore, it is also likely to play a central role in fusion activation by linking CD4 plus chemokine receptor-induced conformational changes in gp120 to gp41 fusogenicity. These gp120 contact residues are present in diverse primate lentiviruses, suggesting conservation of function.

L36 ANSWER 55 OF 73 MEDLINE
92214267 Document Number: 92214267. PubMed ID: 1805558. Structure and function in recombinant HIV-1 gp120 and speculation about the disulfide bonding in the gp120 homologs of HIV-2 and SIV. Gregory T; Hoxie J; Watanabe C; Spellman M. (Dept. of Process Sciences, Genentech, Inc., So. San Francisco, CA 94080.) ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1991) 303 1-14. Journal code: 0121103. ISSN: 0065-2598. Pub. country: United States. Language: English.

L36 ANSWER 60 OF 73 MEDLINE
92030376 Document Number: 92030376. PubMed ID: 1931228. Hypothetical assignment of intrachain disulfide bonds for HIV-2 and SIV envelope glycoproteins. Hoxie J A. (Hematology-Oncology Section, Hospital of University of Pennsylvania, Philadelphia 19104.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1991 Jun) 7 (6) 495-9. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

L36 ANSWER 56 OF 73 MEDLINE
92197002 Document Number: 92197002. PubMed ID: 1549912. Computer predictions of functional, topogenic, and antigenic domains in human immunodeficiency virus-2 envelope glycoprotein. Becker Y. (Department of Molecular Virology, Faculty of Medicine, Hebrew University of Jerusalem, Israel.) VIRUS GENES, (1992 Jan) 6 (1) 79-93. Journal code: 8803967. ISSN: 0920-8569. Pub. country: United States. Language: English.

AB The gp160 of HIV-2 was studied with the aid of computer programs that provide the hydrophilicity, surface probability, flexibility, and antigenicity index of the amino-acid sequence in a polypeptide chain. Such analyses allow the identification of hydrophobic amino-acid domains in the polypeptide chain that may serve as putative proteolytic cleavage signals and putative antigenic domains. It was possible to define the function of hydrophobic domains in the polypeptide chain that serve as signals and amino-acid sequences involved in the transfer of the polypeptide through the cellular membrane by the cellular signal recognition protein (SRP) complex. By comparison to reported properties of HIV-1 gp160 and SIVMAC gp160, it was possible to define antigenic domains in the loops of gp120 resulting from the reported interchain disulfide bonds defining putative antigenic domains specific for HIV-2.

L38 ANSWER 35 OF 105 MEDLINE
2001176559 Document Number: 21029094. PubMed ID: 11188697. Structures of HIV-1 gp120 envelope glycoproteins from laboratory-adapted and primary isolates. Kwong P D; Wyatt R; Majeed S;

Robinson J; Sweet R W; Sodroski J; Hendrickson W A. (Department of Biochemistry and Molecular Biophysics, Columbia University, New York, New York 10032, USA.) STRUCTURE WITH FOLDING & DESIGN, (2000 Dec 15) 8 (12) 1329-39. Journal code: 100889329. ISSN: 0969-2126. Pub. country: England: United Kingdom. Language: English.

AB BACKGROUND: The gp120 exterior envelope glycoprotein of HIV-1 binds sequentially to CD4 and chemokine receptors on cells to initiate virus entry. During natural infection, gp120 is a primary target of the humoral immune response, and it has evolved to resist antibody-mediated neutralization. We previously reported the structure at 2.5 A of a gp120 core from the HXBc2 laboratory-adapted isolate in complex with a 2 domain fragment of CD4 and the antigen binding fragment of a human antibody. This revealed atomic details of gp120-receptor interactions and suggested multiple mechanisms of immune evasion. RESULTS: We have now extended the HXBc2 structure in P222, crystals to 2.2 A. The enhanced resolution enabled a more accurate modeling of less-well-ordered regions and provided conclusive identification of the density in the central cavity at the crux of the gp120-CD4 interaction as isopropanol from the crystallization medium. We have also determined the structure of a gp120 core from the primary clinical HIV-1 isolate, YU2, in the same ternary complex but in a C2 crystal lattice. Comparisons of HXBc2 and YU2 showed that while CD4 binding was rigid, portions of the gp120 core were conformationally flexible; overall differences were minor, with sequence changes concentrated on a surface expected to be exposed on the envelope oligomer. CONCLUSIONS: Despite dramatic antigenic differences between primary and laboratory-adapted HIV -1, the gp120 cores from these isolates are remarkably similar. Taken together with chimeric substitution and sequence analysis, this indicates that neutralization resistance is specified by quaternary interactions involving the major variable loops and thus affords a mechanism for viral adaptation. Conservation of the central cavity suggests the possibility of therapeutic inhibitors. The structures reported here extend in detail and generality our understanding of the biology of the gp120 envelope glycoprotein.

L42 ANSWER 8 OF 8 MEDLINE
1998216721 Document Number: 98216721. PubMed ID: 9557643. Human immunodeficiency virus type 1 attachment to HeLa CD4 cells is CD4 independent and gp120 dependent and requires cell surface heparans. Mondor I; Ugolini S; Sattentau Q J. (Centre d'Immunologie de Marseille-Luminy, Marseille, France.) JOURNAL OF VIROLOGY, (1998 May) 72 (5) 3623-34. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The binding of human immunodeficiency virus type 1 (HIV-1) (Hx10) virions to two different cell lines was analyzed by using a novel assay based on the detection, by anti-HLA-DR-specific antibodies, of HLA-DR+ virus binding to HLA-DR- cells. Virion attachment to the CD4+-T-cell line A3.01 was highly CD4 dependent in that it was potently inhibited by CD4 monoclonal antibodies (MAbs), and little virus binding to the CD4- sister A2.01 line was observed. By contrast, virion binding to HeLa cells expressing moderate or high levels of CD4 was equivalent to, or lower than, binding to wild-type CD4- HeLa cells. Moreover, several CD4 MAbs did not reduce, but enhanced, HIV-1 attachment to HeLa-CD4 cells. CD4 was required for infection of HeLa cells, however, demonstrating a postattachment role for this receptor. MAbs specific for the V2 and V3 loops and the CD4i epitope of gp120 strongly inhibited virion binding to HeLa-CD4 cells, whereas MAbs specific for the CD4bs and the

2G12 epitopes enhanced attachment. Despite this, all gp120- and gp41-specific MAbs tested neutralized infectivity on HeLa-CD4 cells. HIV-1 attachment to HeLa cells was only partially inhibited by MAbs specific for adhesion molecules present on the virus or target cells but was completely blocked by polyanions such as heparin, dextran sulfate, and pentosan sulfate. Treatment of HeLa-CD4 cells with heparinases completely eliminated HIV attachment and infection, strongly implicating cell surface heparans in the attachment process. CD4 dependence for HIV-1 attachment to target cells is thus highly cell line specific and may be replaced by other ligand-receptor interactions.

L44 ANSWER 35 OF 35 MEDLINE
91087281 Document Number: 91087281. PubMed ID: 1985197. Identification of the principal neutralizing determinant of human immunodeficiency virus type 1 as a fusion domain. Freed E O; Myers D J; Risser R. (McArdle Laboratory for Cancer Research, University of Wisconsin, Madison 53706.) JOURNAL OF VIROLOGY, (1991 Jan) 65 (1) 190-4. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The V3 loop, located near the middle of the surface envelope glycoprotein gp120, is the major neutralizing domain of human immunodeficiency virus type 1 (HIV-1). Although the majority of the V3 loop is highly variable between different strains of HIV-1, a Gly-Pro-Gly-Arg motif at the tip of the loop is highly conserved. To determine whether this region plays a role in fusion mediated by the HIV-1 envelope glycoproteins, we introduced **seven single-amino-acid changes in the V3 loop.** The mutant envelope glycoproteins were expressed from an HIV-1 envelope expression vector and analyzed for their ability to induce cell fusion in the absence of virus replication. Our results indicated that **single-amino-acid changes in the V3 loop were capable of completely abolishing or greatly reducing the ability of the HIV-1 envelope glycoproteins to induce cell fusion,** thereby identifying the V3 loop as a fusion domain of HIV-1. Mutations in the highly conserved tip of the loop or in a nonconserved region flanking the highly conserved tip had no effect on envelope glycoprotein synthesis, processing, transport, or binding to the CD4 receptor molecule. Mutation of the putative disulfide bridge-forming Cys at residue 336 blocked gp160 cleavage and CD4 binding.

L44 ANSWER 34 OF 35 MEDLINE
92015517 Document Number: 92015517. PubMed ID: 1717717. Characterization of a discontinuous human immunodeficiency virus type 1 gp120 epitope recognized by a broadly reactive neutralizing human monoclonal antibody. Thali M; Olshevsky U; Furman C; Gabuzda D; Posner M; Sodroski J. (Department of Pathology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115.) JOURNAL OF VIROLOGY, (1991 Nov) 65 (11) 6188-93. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB While one hypervariable, linear neutralizing determinant on the human immunodeficiency virus type 1 (HIV-1) gp120 envelope glycoprotein has been well characterized, little is known about the conserved, discontinuous gp120 epitopes recognized by neutralizing antibodies in infected individuals. Here, the epitope recognized by a broadly reactive

neutralizing monoclonal antibody (F105) derived from an HIV -1-infected patient was characterized by examining the effects of changes in conserved gp120 amino acids on antibody reactivity. **The F105 epitope was disrupted by changes in gp120 amino acids 256 and 257, 368 to 370, 421, and 470 to 484**, which is consistent with the discontinuous nature of the epitope. Three of these regions are proximal to those previously shown to be important for CD4 binding, which is consistent with the ability of the F105 antibody to block gp120 -CD4 interaction. Since F105 recognition was more sensitive to amino acid changes in each of the four identified gp120 regions than was envelope glycoprotein function, replication-competent mutant viruses that escaped neutralization by the F105 antibody were identified. These studies identify a conserved, functional HIV-1 gp120 epitope that is immunogenic in man and may serve as a target for therapeutic or prophylactic intervention.

L44 ANSWER 32 OF 35 MEDLINE
92410588 Document Number: 92410588. PubMed ID: 1382339. Amino acid residues of the human immunodeficiency virus type I gp120 critical for the binding of rat and human neutralizing antibodies that block the gp120-sCD4 interaction. McKeating J A; Thali M; Furman C; Karwowska S; Gorny M K; Cordell J; Zolla-Pazner S; Sodroski J; Weiss R A. (Institute of Cancer Research, Chester Beatty Laboratories, London, U.K.) VIROLOGY, (1992 Sep) 190 (1) 134-42. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB We have characterized the discontinuous epitopes recognized by two rat and three human neutralizing monoclonal antibodies (mAb) by examining the effect of single amino acid changes in conserved residues of gp120 on mAb recognition. A human mAb derived from an infected individual, 448D, and two rat mAbs, 39.13g and 39.3b, respectively, derived by immunization with native recombinant gp120, recognize similar epitopes. **Recognition of the envelope glycoproteins by these mAbs was affected by changes in gp120 amino acid residues 88, 113, 117, 257, 368, or 370.** The gp120 amino acids 257, 368, and 370 have previously been reported to be important for CD4 binding, which is consistent with the ability of these mAbs to block the gp120-CD4 interaction. Residues 88, 113, and 117 are not thought to be important for CD4 binding, suggesting that the antibody epitopes overlap, but are distinct from, the CD4 binding region. We also found that some **alterations in gp120 residues 88, 117, 368, or 421 reduced the ability of polyclonal sera from HIV-1-infected individuals to inhibit the interaction of the mutant gp120 glycoproteins with soluble CD4.** Thus, changes in the HIV-1 gp120 glycoprotein that minimally affect the receptor binding may allow escape from neutralizing antibodies directed against the CD4 binding region.

L44 ANSWER 27 OF 35 MEDLINE
93287215 Document Number: 93287215. PubMed ID: 7685405. Characterization of conserved human immunodeficiency virus type 1 gp120 neutralization epitopes exposed upon gp120 -CD4 binding. Thali M; Moore J P; Furman C; Charles M; Ho D D; Robinson J; Sodroski J. (Department of Pathology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts.) JOURNAL OF VIROLOGY, (1993 Jul) 67 (7) 3978-88. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Interaction with the CD4 receptor enhances the exposure on the human immunodeficiency type 1 gp120 exterior envelope glycoprotein of conserved, conformation-dependent epitopes recognized by the 17b and 48d neutralizing monoclonal antibodies. The 17b and 48d antibodies compete with anti-CD4 binding antibodies such as 15e or 21h, which recognize discontinuous gp120 sequences near the CD4 binding region. To characterize the 17b and 48d epitopes, a panel of human immunodeficiency virus type 1 gp120 mutants was tested for recognition by these antibodies in the absence or presence of soluble CD4. **Single amino acid changes in five discontinuous, conserved, and generally hydrophobic regions of the gp120 glycoprotein resulted in decreased recognition and neutralization by the 17b and 48d antibodies.** Some of these regions overlap those previously shown to be important for binding of the 15e and 21h antibodies or for CD4 binding. These results suggest that discontinuous, conserved epitopes proximal to the binding sites for both CD4 and anti-CD4 binding antibodies become better exposed upon CD4 binding and can serve as targets for neutralizing antibodies.

L44 ANSWER 24 OF 35 MEDLINE
93353643 Document Number: 93353643. PubMed ID: 8350416. Evidence that the structural conformation of envelope gp120 affects human immunodeficiency virus type 1 infectivity, host range, and syncytium-forming ability. Stamatatos L; Cheng-Mayer C. (Cancer Research Institute, School of Medicine, University of California, San Francisco 94143-0128.) JOURNAL OF VIROLOGY, (1993 Sep) 67 (9) 5635-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We investigated how amino acid changes within and outside the V3 loop of the envelope glycoprotein of human immunodeficiency virus type 1 influence the infectivity, host range, and syncytium-forming ability of the virus. Our studies show that on the genomic backgrounds of the human immunodeficiency virus type 1 strains SF2 and SF13, a reciprocal exchange of full-loop sequences does not alter the syncytium-forming ability of the viruses, indicating that a determinant(s) for this biological property maps outside the loop. However, **specific amino acid substitutions, both within and outside the V3 loop, resulted in loss of infectivity, host range, and syncytium-forming potential of the virus.** Furthermore, it appears that a functional interaction of the V3 loop with regions in the C2 domain of envelope gp120 plays a role in determining these biological properties. Structural studies of mutant glycoproteins show that the mutations introduced affect the proper association of gp120 with the transmembrane glycoprotein gp41. Our results suggest that mutations that alter the structure of the V3 loop can affect the overall conformation of gp120 and that, reciprocally, the structure of the V3 loop is influenced by the conformation of other regions of gp120. Since the changes in the replicative potential, host range, and fusogenic ability of the mutant viruses correlate well with the changes in gp120 conformation, as monitored by the association of gp120 with gp41, our results support a close relationship between envelope gp120 structural conformation and the biological phenotype of the virus.